Modulation of cell signaling networks after CTLA4 blockade in patients with metastatic melanoma.

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Public Summary:
The effects of anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA4) on cell signaling networks were studied in peripheral blood mononuclear cell (PBMC) samples from patients with metastatic melanoma treated with the monoclonal blocking antibody tremelimumab. Intracellular flow cytometry was used to detect phosphorylated (p; ie. activated) signaling molecules downstream of the T cell receptor (TCR) and cytokine receptors. PBMC from tremelimumab-treated patients were characterized by an increase in the downstream signaling molecules pp38, pSTAT1 and pSTAT3, and a decrease in pLck, pERK1/2 and pSTAT5 levels. These changes were noted in CD4 and CD8 T lymphocytes but also in CD14 monocytes. A divergent pattern of phosphorylation of Zap70, LAT, Akt and STAT6 was noted in patients with or without an objective tumor response. The administration of the CTLA4-blocking antibody tremelimumab to patients with metastatic melanoma influences signaling networks downstream of the TCR and cytokine receptors both in T cells and monocytes. The strong modulation of signaling networks in monocytes suggests that this cell subset may be involved in clinical responses to CTLA4 blockade.

Scientific Abstract:
BACKGROUND: The effects on cell signalling networks upon blockade of cytotoxic T lymphocyte-associated antigen-4 (CTLA4) using the monoclonal antibody tremelimumab were studied in peripheral blood mononuclear cell (PBMC) samples from patients with metastatic melanoma. METHODOLOGY/PRINCIPAL: Findings Intracellular flow cytometry was used to detect phosphorylated (p) signaling molecules downstream of the T cell receptor (TCR) and cytokine receptors. PBMC from tremelimumab-treated patients were characterized by increase in pp38, pSTAT1 and pSTAT3, and decrease in pLck, pERK1/2 and pSTAT5 levels. These changes were noted in CD4 and CD8 T lymphocytes but also in CD14 monocytes. A divergent pattern of phosphorylation of Zap70, LAT, Akt and STAT6 was noted in patients with or without an objective tumor response. CONCLUSIONS/SIGNIFICANCE: The administration of the CTLA4-blocking antibody tremelimumab to patients with metastatic melanoma influences signaling networks downstream of the TCR and cytokine receptors both in T cells and monocytes. The strong modulation of signaling networks in monocytes suggests that this cell subset may be involved in clinical responses to CTLA4 blockade. CLINICAL TRIAL REGISTRATION: clinicaltrials.gov; Registration numbers NCT00090896 and NCT00471887.